REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 8-11 are pending in the application and presented for examination. Claims 1-7 are canceled without prejudice. Claims 9 and 10 are original and unchanged. Claims 8 and 11 are currently amended to set forth preferred embodiments of the invention in which the inventive method utilizes certain alkyl-L-carnitines having the structure as disclosed in Figure 1 of the specification. Support for the amendment to claims 8 and 11 is found in Figure 1 and paragraphs [0007], [0016] and [0017] of the specification. No new matter has been introduced in the amended claim set or any other portion of the present amendment. Reconsideration is respectfully requested in view of the amendment to the claims and the following remarks.

I. THE INVENTION

The present invention relies on the discovery of novel liposomal formulations of L-carnitine derivatives and methods of using these derivatives for treating peripheral arterial disease, a common type of peripheral vascular disease. The amended claim set is focused on the use of liposomal formulations of certain alkyl-L-carnitines for the treatment of peripheral arterial disease.

II. REJECTIONS UNDER 35 U.S.C. §102

In the Office Action, claims 6 and 7 stand rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Pat. No. 4,866,040 to Stracher *et al.*; claims 1 and 5 stand rejected under 35 U.S.C. §102(a) as allegedly being anticipated by U.S. Pub. No. 2002/0039595 to Keller ("Keller '595"); and claims 1 and 5 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Pat. No. 6,726,924 to Keller ("Keller '924"). Applicant believes that these rejections are rendered moot in view of the cancellation of claims 1, 5, 6 and 7.

III. REJECTIONS UNDER 35 U.S.C. §103(a)

1. First Rejection Under 35 U.S.C. §103(a)

Claims 1-11 stand rejected under 35 U.S.C. §103(a), as allegedly being obvious over U.S. Pat. No. 5,747,536 to Cavazza, alone or in combination with Keller '924 and U.S. Pat.

No. 5,993,851 to Foldvari ("Foldvari"). In this regard, the Examiner alleges that Cavazza discloses L-carnitine and L-carnitine derivatives for the treatment of peripheral vascular diseases and further alleges that Keller '924 discloses that the bioavailability of L-carnitine is increased when administered in a liposomal formulation. Moreover, the Examiner further cites Foldvari for allegedly teaching that liposomal encapsulation of biologically active agents alters the pharmacokinetic fate of the active agent. Therefore, the Examiner is of the opinion that the invention is obvious over these references, alone or combined. To the extent that the rejection is applicable to the currently amended claim set, Applicant respectfully traverses the rejection. Applicant notes that claims 1-7 are canceled in the present amendment and therefore the rejection of claims 1-7 is now moot.

NO PRIMA FACIE CASE OF OBVIOUSNESS EXISTS

Applicant respectfully points out that the amended claims are currently focused on the method of using certain alkyl-L-carnitine derivatives in a liposomal formulation for the treatment of peripheral arterial diseases, and asserts that a *prima facie* case of obviousness has not been established for the presently claimed invention. To establish a *prima facie* case of obviousness, 3 basic criteria must be met:

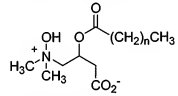
> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicant respectfully submits that a *prima facie* case of obviousness has not been established because there is no suggestion or motivation to modify the cited reference; and the cited references do not teach all the claimed limitations.

There is No Suggestion or Motivation to Modify the Cited References.

Applicant states that there is simply no motivation or suggestion provided in the cited references to modify their teaching in the way the Examiner has contemplated. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

As discussed above, the claims now pending in the application are focused on the use of a liposomal formulation comprising certain alkyl-L-carnitines as the active agent for treating peripheral arterial disease. Specifically, the presently claimed method, as set forth in amended claim 8, recites:

> Claim 8. (Currently amended) A method for treating a peripheral arterial disease in a mammal, said method comprising:
> administering a therapeutically effective amount of a liposomal formulation of a L-carnitine derivative, wherein ***said L-carnitine derivative is an alkyl-L-carnitine of formula***
>
> 
>
>
> ***wherein n is an integer selected from the group consisting of 0, 4, 6, 8, 10, 12, 14 and 16***, thereby treating a peripheral arterial disease in said mammal.

Applicant respectfully asserts that none of the cited references teach or suggest using an alkyl-L-carnitine, having the formula shown above, as the active agent in a liposomal formulation for treating peripheral arterial disease. In stark contrast to the present invention, the cited reference, Cavazza, is for the use of a pharmaceutical composition comprising a ***combination*** of L-carnitine (or derivatives thereof) ***and*** trihydroxy- or tetrahydroxy-stilbene (*see*, Title, Cavazza). Cavazza describes that the ***combination*** of active agents (*i.e.*, L-carnitine (or derivatives thereof) with trihydroxy- or tetrahydroxy-stilbene) exhibits synergistic

pharmacologic effects to inhibit platelet aggregation and may be useful in treating cardiovascular diseases, peripheral vascular diseases, and diabetic peripheral neuropathy. In view of the teaching of Cavazza, Applicant respectfully asserts that a skilled artisan would not be motivated to modify Cavazza to arrive at the presently claimed invention as Cavazza simply does not suggest using alkyl-L-carnitines ***alone*** as the active agent in a pharmaceutical composition, much less in a liposomal formulation for the treatment of peripheral arterial disease as is presently claimed by Applicant.

The Prior Art Disclosures Teaches Away From the Claimed Invention

A prior art reference must be considered in its entirety, *i.e.,* as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469, U.S. (1984).

Further to the above, Applicant respectfully asserts that Cavazza actually ***teaches away*** from the use of a pharmaceutical composition comprising alkyl-L-carnitine alone as the active agent for the treatment of peripheral arterial disease as presently claimed. Cavazza describes that the pathological basis of cardiovascular diseases, peripheral vascular diseases and diabetic peripheral neuropathy is undesired platelet aggregation. Cavazza performed *in vitro* platelet aggregation tests to quantify the inhibitory effects of, *inter alia*, L-carnitine alone, resveratrol alone (a trihydroxy-stilbene), and combination thereof on platelet aggregation and used these results to evaluate the potential effectiveness of these compounds for treating various disease, including cardiovascular diseases, peripheral vascular diseases, and diabetic peripheral neuropathy. In short, Cavazza discloses that L-carnitine, when used by itself, was ***completely ineffective*** at inhibiting platelet aggregation. The disclosure of Cavazza would clearly suggest to a skilled artisan that a composition comprising L-carnitine alone ***is not*** effective at treating the aforementioned diseases since Cavazza clearly teaches that L-carnitine (or derivatives thereof) alone does not inhibit platelet aggregation. Specifically, Cavazza teaches at column 4, lines 51-62:

> "[Platelet] [a]ggregation was measured in basal conditions and after 10 minutes of incubation with L-carnitine, resveratrol, grape extract, and combinations of these preparations. ***Inhibition of the platelet aggregation induced by collagen (2.5 ng/ml) proved evident (ED_{50} 3.5 ng/ml) for resveratrol and for grape extract (ED_{50} with a resveratrol concentration equal to 2.5 ng/l), whereas for carnitine or its derivatives there was no significant change.*** However, when using a combination of the carnitines plus resveratrol at the same doses, 100% inhibition of platelet aggregation was achieved, thus showing a marked synergism between L-carnitine and resveratrol or grape extract containing resveratrol." [Emphasis added.]

As stated above, Cavazza clearly discloses that L-carnitine (or derivatives thereof) alone ***would not*** be effective in treating peripheral vascular diseases such as peripheral arterial disease as is presently claimed by Applicant, and actually ***teaches away*** from this use.

Moreover, this deficiency of Cavazza is not supplemented by Keller '924 or Foldvari. Keller '924 describes an oral liposomal delivery system, which is a liposome-capsule dosage system, *i.e.* a "Lipocap." *See*, Abstract, Keller. Keller '924 discloses preparing a lipocap formulation of L-carnitine, but does not teach or use L-carnitine derivatives, such as the presently claimed alkyl-L-carnitine derivatives, for treating peripheral arterial disease. Foldvari also does not describe a liposomal formulation comprising alkyl-L-carnitines as the active agent and therefore also does not address the deficiency of Cavazza.

In view of the above, Applicant respectfully submits that a skilled artisan, having possession of the cited references, would not be motivated to modify the references to arrive at the presently claimed invention as none of the cited references teach or suggest treating peripheral arterial disease using certain alkyl-L-carnitines as *the* active agent, much less a liposomal formulation of these alkyl-L-carnitines as is presently claimed by Applicant. As such, Applicant respectfully asserts that the presently claimed invention as set forth in claims 8-11 is not obvious over the cited references and respectfully request that the rejection be withdrawn.

2. Second rejection Under 35 U.S.C. §103(a)

Claims 1, 4-6, 8-10 also stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Pat. No. 4,968,719 to Brevetti ("Brevetti"), in view of Keller '924 and/or Foldvari; or vice versa, that is over Keller '924 and/or Foldvari in view of Brevetti. More particularly, the Examiner is of the opinion that the combination of references renders obvious the claimed invention of liposomal formulations comprising specifically the compound L-carnitine, and methods of using such formulations for treating peripheral arterial disease. Insofar as the rejection is applicable to the amended claim, Applicant respectfully traverses the rejection. Applicant notes that claims 1, 4-6 are canceled in this amendment and believes that the rejection of these claims is now moot.

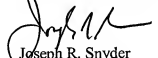
In an earnest effort to advance prosecution of the instant application, Applicant has amended the claim set to focus on one preferred aspect the invention of using certain alkyl-L-carnitines (8 compounds total), having the formula as set forth in Figure 1, for the treatment of peripheral arterial disease. Applicant respectfully points out that many of the presently claimed compounds are those previously set forth in the dependent claims (*i.e.*, claims 2, 3, 11) that were not cited as part of this rejection. Applicant respectfully notes that none of the cited references teaches or suggests using the presently claimed alkyl-L-carnitines for treating peripheral arterial disease, and as such, Applicant believes that the cited references alone or when combined do not render obvious the claimed invention. In view of the above, Applicant respectfully requests that the rejection of the pending claims, *i.e.*, claims 8-11, be withdrawn, and urges the Examiner to send this application to issue.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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